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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,764	11/15/2000	Heinz-Josef Lenz	064189-0201	7045

38706 7590 10/26/2007

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	
MAIL DATE	**DELIVERY MODE**
10/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/715,764	LENZ ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,48,52,53,56,61-66 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,48,52,53,56,61-66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/07,4/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendments filed on July 18, 2007 and April 17, 2007. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 47-48, 52, 53, 56, 61-66 and 68-70 are currently pending and have been examined herein.

2. The examiner reviewing your application at the PTO has changed. To aid in correlating papers in this application, all further correspondence regarding this application should be directed to examiner Carla Myers.

3. The following rejections were originally presented in the Office action of October 13, 2006 and has been modified to accommodate the amendments to the claims:

Claim Rejections - 35 USC § 112 - Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 48, 52, 56, 61-66, and 68-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for screening a human subject for sensitivity to 5-FU comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating said genotype to the subject's sensitivity to 5-FU, does not reasonably provide enablement for screening any subject for sensitivity to any

TS-directed chemotherapeutic drug comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating said genotype to said sensitivity to said TS-directed chemotherapeutic drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claims 47, 48, 52, 56, and 61-66 broadly encompass screening a subject for sensitivity to any TS-directed chemotherapeutic drug by genotyping the subject's 28 base repeat in the 5' UTR of thymidylate synthase (TS) and correlating the genotype to sensitivity to the drug. Claims 68-71 further encompass screening any non-human colorectal cancer patient for sensitivity to fluoropyrimidine by assaying for the presence of a 28 bp tandem repeat in the 5' UTR of the TS gene.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The specification teaches a study which correlated a human subject's thymidylate synthase 5'UTR 28 base pair repeat genotype with TS mRNA expression in normal and tumor cells (see pages 14-15). Further, the art teaches a correlation between TS mRNA expression and sensitivity to 5-FU. The specification teaches (page 5) that TS is the enzyme that catalyzes the intracellular methylation of dUMP to dTMP, which is the sole *de novo* source of thymidylate, and is a critical target for 5-fluorouracil which binds to TS and inhibits the conversion of dUMP to dTMP. The specification teaches that therefore, sensitivity or resistance to 5-FU is dependent on levels of TS in tumors. Accordingly, the specification is enabling for a method for screening a human subject for sensitivity to 5-FU comprising determining the genotype of a subject's biological sample at a tandemly repeated 28 base pair repeat in the 5' UTR of a TS gene in the sample and correlating said genotype to said sensitivity to 5-FU.

However, the specification broadly defines "TS-directed drug" to encompass drugs that involve or are targeted against, or are based on thymidylate synthase. This encompasses an extremely large group of drugs, including any fluoropyrimidine, which have not been taught by the specification. The specification provides no universal correlation that any drug which involves, targets, or is based on TS would be sensitive to the levels of TS in tumors. Without such guidance the skilled artisan would be unable to predictably determine which other TS directed drugs would also be associated with

sensitivity to chemotherapy given that the claims encompass a large class of drugs which are not functionally related and the specification provides no guidance as to other classes of drugs which would function in the same manner as a fluoropyrimidine. The large genus of drugs that "are based" on TS or involve TS, or even target TS, as encompassed by the claims, would not be expected to do so by the same mechanism as a 5-FU which specifically binds to and inhibits TS. The claimed drugs include a large genus of drugs which are structurally and different from each other and from 5-FU.

Additionally, claims 68-70 encompass screening in any colorectal patient, which includes other mammals such as dogs, but the specification only provides analysis of the TS 5'UTR 28 base pair repeat in humans. The specification provides no guidance as to whether the repeat occurs in other species, such as dogs.

Papamichael (The Oncologist, vol. 4, 1999, pages 478-487) teaches that 5-FU is characterized by marked schedule dependency in both the quality and quantity of its effects (page 480). Papamichael teaches that a number of other fluoropyrimidines have been synthesized, such as doxifluridine which must have its ribosyl group removed by the enzyme uridine phosphorylase to produce 5-FU (page 482, col. 1, 2nd full para). Papamichael teaches that this enzyme is reported to be more activity in some tumor cells than in normal tissues, resulting in an improved ratio in tumor bearing mice, but that very high activity is found in normal human liver casting doubt on doxyfluridine's claimed sensitivity.

To identify and determine which drugs encompassed by the broad scope of the claims would be associated with an sensitivity based on the TS polymorphism of any

subject would require extensive experimentation which, given the lack of guidance in the specification, would essentially be random, trial by error experimentation, which is considered to be undue. While methods for identifying polymorphisms are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may linked to a disease or therapeutic response. The results of performing such methodology is highly unpredictable. The specification does not provide a predictable means for identifying additional drugs which are associated with sensitivity based on the TS genotype of any subject. The art of determining an association between a polymorphism and response to treatment is highly unpredictable. An association between a polymorphism and treatment response to one type of drug does not allow one to reasonably predict whether the polymorphism will also be associated with responses to other types of drugs. Accordingly, there is no predictable means for ascertaining a priori whether the TS genotype will be associated with sensitivity using other types of "TS directed" chemotherapeutic drugs, as is broadly defined by the specification.

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only an association between the TS 5'UTR 28 base pair repeat polymorphism in humans and sensitivity to 5-FU whereas the claims encompass using the TS genotype to correlate sensitivity to any type of TS directed chemotherapeutic drug in any species. The specification has not taught that the TS genotype is associated with a representative number of different types of TS directed chemotherapeutic drugs as is broadly defined. As set forth above, in view of

the unpredictability in the art, extensive experimentation would be required to determine whether the TS 5'UTR 28 base pair repeat polymorphism is associated with sensitivity to any fluoropyrimidine let alone any "TS directed chemotherapeutic drug". Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Arguments

5. The response traverses the rejection by stating that the specification defines a "TS-directed drug" as a drug that involves or targets against or is based on thymidylate synthase (TS). It is asserted that the action of TS-directed drugs were well known at the time the invention was made, as were alternatives of 5-FU having the same or similar mechanisms of action. The response states that Papamichael teaches 5-FU analogs. Applicants conclude that because the mechanism of action of 5-FU was known and because drugs having the same or a similar mechanism of action as 5-FU were also known, undue experimentation would not be required to identify patients sensitive to drugs other than 5-FU.

Applicants arguments have been fully considered but are not persuasive. The specification has established a correlation between the 28bp tandem repeat in the 5' UTR of the TS gene and sensitivity to the drug 5-FU. The specification has not established that the presence of the 28bp tandem repeat confers sensitivity to any other chemotherapeutic drugs. As set forth in the specification, the mechanism by which 5-FU

acts requires the binding of 5-FU to TS, leading to the inhibition of the conversion of dUMP to dTMP. However, the present claims are not limited to TS-directed chemotherapeutic drugs which act by this same mechanism. Rather, the claims encompass any "TS-directed chemotherapeutic drug." Such drugs include any agent that is by some means involved in or targeted against, or "based" on thymidylate synthase. This encompasses a significantly large genus of drugs that differ in their structure and their functional activity. Such drugs may include antisense molecules, ribozymes, small molecules, antibodies etc which alter TS expression or activity, directly or indirectly. Thus, the claims encompass chemotherapeutic agents which would not be expected to act by the same mechanism as a 5-FU – i.e., drugs which do not specifically bind to TS and which do not specifically inhibit the conversion of dUMP to dTMP to the same degree as that which occurs with 5-FU. Yet, the specification has not established in general that the presence of a double repeat of the 28bp tandem repeat is correlated with sensitivity to any drug which directly or indirectly effects, to any level, the expression or activity of TS. Regarding fluropyrimidine compounds, the specification has also not established that a representative number of compounds encompassed by this genus of compounds act by the same mechanism as 5-FU. As discussed in the above rejection, Papamichael teaches that 5-FU is characterized by marked schedule dependency in both the quality and quantity of its effects (page 480). Papamichael teaches that fluoropyrmidines have different mechanisms of activity and different degrees of effectiveness. For example, the fluoropyrimidine doxifluridine must have its ribosyl group removed by the enzyme uridine phosphorylase to produce 5-FU (page

482, col. 1, 2nd full para). Papamichael teaches that this enzyme is reported to be more activity in some tumor cells than in normal tissues, resulting in an improved ratio in tumor bearing mice, but that very high activity is found in normal human liver casting doubt on doxyfluridine's claimed sensitivity. Thereby, the results obtained with 5-FU cannot be extrapolated to all fluoropyrmidine drugs because it has not been established that 5-FU derivatives, such as doxifluridine, will also alter a patient's sensitivity to therapy based on the presence or absence of the 28bp tandemly repeated sequence in the 5' UTR of the TS gene.

The response further states that the pending claims are directed to screening a biological sample isolated from a human patient. However, claims 68-70 do not in fact recite this limitation. Rather, claims 68-70 encompass assaying a biological sample from a colorectal cancer patient. Thereby, the claims encompass assaying a biological sample obtained from any non-human organism having colorectal cancer. However, the specification has not established that a representative number of non-human subjects have a variable number of the 28 bp tandemly repeated sequences in the 5'UTR of the TS gene and has not established a correlation between such repeat sequences and sensitivity to fluoropyrimidine in a representative number of non-human colorectal cancer patients.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47, 48, 52, 53, 56, 64 and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano,

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie teaches detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-

fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to TS directed chemotherapy drugs. The ordinary artisan would have been motivated to

determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create a prognostic test for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

Regarding claim 70, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Horie so as to have treated those patients identified as being sensitive to 5-FU by administering 5-FU therapy in order to have provided an effective means for treating colorectal cancer.

7. Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The teachings of Horie and Leichman in view of Ruano are set forth above. Horie and Leichman in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug.

Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, , and 4) TS genotype could be determined for a subject from normal cells, it would have been prima facie obvious to the ordinary

artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

8. Claims 47, 48, 52, 53, 56, 64 and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman and Kawakami (Kawakami et al; Proc. Annu. Meet. Am. Soc. Clin. Oncol. Vol. 17, pp A1128, May 1998) in view of Ruano.

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie teaches detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para).

Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for

determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Additionally, Kawakami teaches investigating the association between the TS 5' UTR tandemly repeated sequence and expression of TS in cancers. Kawakami teaches that double and triple repeats were found, along with one quadruple and one penta repeated sequence, and that patients were predominantly either heterozygous for the double and triple repeat (18), or homozygous for the triple repeat (46), and that two patients were homozygous for the triple repeat. Kawakami teaches that TS expression correlated with the number of repeats and teaches a level of 1.07 for the 2R/2R genotype, 1.38 for the 2R/3R genotype, and 2.59 for the 3RI/3R genotype.

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and

that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Kawakami and Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to 5-FU. The ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer or gastrointestinal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create prognostic tests for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU, that Horie teaches that 1) TS expression is associated with the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract,

and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, that Kawakami teaches that the 5' UTR repeat genotype correlated with TS expression levels in gastrointestinal tumors, and that Ruano provides motivation for associating a patient's genotype with sensitivity to therapy, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a human subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

9. Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman and Kawakami in view of Ruano, as applied to claims 47-48, 50, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The teachings of Horie and Leichman and Kawakami in view of Ruano are set forth above. Horie and Leichman and Kawakami in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for

both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug.

Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU, that Horie teaches that 1) TS expression is associated to the number

of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, , and 4) TS genotype could be determined for a subject from normal cells, that Kawakami teaches that the 5' UTR repeat genotype correlated with TS expression levels in gastrointestinal tumors, and that Ruano provides motivation for associating a patient's genotype with sensitivity to therapy, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a human subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal or gastrointestinal cancer.

Response to Arguments

10. The response traverses the rejection and asserts that Applicant's previous arguments are incorporated by reference. As all previous arguments have been addressed, the responses to arguments from previous office actions are maintained.

The response asserts that Horie does not teach what the Office suggests in that the results of Horie were obtained using an artificial *in vitro* system linking a polymorphic 5' UTR TS promoter to a reporter CAT gene. It is asserted that Horie does not provide

TS expression data in a sample isolated from a patient. These arguments have been fully considered but are not persuasive. While Horie does not directly assay the TS expression levels in a patient sample, the quantitative CAT assay employed by Horie is an art recognized assay for evaluating expression levels. As such, the findings of Horie regarding the CAT assay would be accepted by those of ordinary skill in the art as reflective of the effect of the polymorphic TS 5' URT on expression levels. Thereby, it is maintained that Horie does in fact teach that the number of 5' UTR TS repeat sequences are correlated with TS expression levels.

The response cites Horie (page 196) as stating that "At present, it is not clear whether the polymorphism-related difference in the transient expression assay affects the biological systems that involve the TS enzyme. Further studies are needed to clarify the effects of the variable number of repetitions in the unique structure of the hTS gene on biological systems." Applicants conclude that this passage acknowledges the limitations that the authors themselves placed on the interpretation of the results reported therein. Applicants assert that "Horie cautions that this reported data is not predictive of what may occur in a true biological system." However, Applicants have not accurately characterized the cited teachings of Horie. Horie does not indicate that the results obtained with the CAT assay would not predictive of *in situ* results. Rather, Horie acknowledges only that the overall biological effect of the different number of TS repeats has not yet been determined. The cited statements of Horie were made in the context of the effect of the number of repeats on disease. Specifically, Horie states that variability in the number of repeats is often associated with an inherited disease, but the

polymorphism in the repeated 5'UTR sequences was detected in normal human individuals and that "there are no data to suggest that the polymorphism might be related to any abnormal physical condition." Thus, Horie teaches that further research would be required to ascertain the association between the observed change in expression level (i.e., the polymorphism in the TS 5' UTR) and a particular physiological condition. As set forth above, Leichman provides this additional information since Leichman teaches that expression levels of TS are correlated to sensitivity to 5-FU in cancer patients.

Applicants state that because Horie does not teach that the polymorphism in the 5'UTR correlates to TS expression in a patient sample, one of skill in the art would not have been motivated to combine the references with any reasonable expectation of success. This argument is also not persuasive because the *in vitro* CAT reporter assay is an art recognized assay known to provide expression results that are predictive of that which would be obtained *in situ*. Applicants have not provided any evidence to substantiate an assertion that the results obtained by Horie using a CAT reporter assay are not reflective of the results obtained in situ using a patient sample. Given that the CAT reporter assay is a well recognized assay to determine the effect of a promoter on expression levels, the ordinary artisan would have had more than a reasonable expectation of success of extrapolating the results obtained with the CAT assay to a sample obtained from a patient. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The response states that the rejection is based on knowledge learned from Applicant's disclosure. The response points to page 21 of the prior Office action in support of this assertion, and to the statement: "[Applicants'] specification states 'Patients with triple repeat in the TS gene as expected from in vitro models had higher gene expression levels." It is asserted that this statement comes from Applicant's own work and cannot be used in framing a rejection under 103. These arguments have been fully considered but are not persuasive. The cited statement on page 21 of the prior Office action has been taken out of context. This statement was made only with respect to the Declaration of Dr. Danenberg. A complete reading of the Office action at page 21 indicates that the Office stated only that the Declaration of Dr. Danenberg included statements which contradict statements made in the specification, particularly with respect to the teaching that "Patients with triple repeat in the TS gene as expected from in vitro models had higher gene expression levels." As previously discussed, Applicants themselves relied heavily upon *in vitro* data to establish the correlation between TS expression levels and the number of TS 5' UTR repeats. Thereby, it is contradictory for Applicants to now assert that *in vitro* expression data is not predictive of *in vivo* expression data.

Applicants point to the previously filed declaration under 37 C.F.R. 1.132 by Dr. Peter V. Danenberg, and assert that this declaration establishes that the system employed by the present inventors is distinct from that employed by Horie. It is asserted that no evidence is required to substantiate the statements made in this declaration. However, while the present inventors employed a methodology distinct from that of Horie, this does not negate the findings of Horie. Again, Horie teaches that, as

determined using a CAT reporter assay, the number of tandem TS 5' UTR repeats is correlated with expression of TS.

Regarding the Leichman reference, the response asserts that Leichman teaches that overexpression of TS was found in some, but not in all patient tumor samples. It is asserted that the authors acknowledge the limitations of the data. In support of this statement, the response points to page 3227 of Leichman as stating that the method has "limitations that preclude exact assessment of intratumoral TS." These arguments have been fully considered but are not persuasive. An "exact assessment of intratumor TS" is not required to establish the obviousness of the claimed invention. Leichman (abstract and page 3228, col. 1) clearly teaches that there is a statistically significant association between TS mRNA and protein levels and response to 5-FU treatment. Although other factors may also contribute to response to 5-FU, this does not negate the essential finding of Leichman of an association between TS expression levels and response to 5-FU. Again, obviousness does not require absolute predictability. In the present situation, the clear teachings of Horie of an association between the number of TS 5'UTR repeats and TS expression levels and the teachings of Leichman of an association between TS expression levels and response to 5-FU, would have lead the ordinary artisan to a method of screening patients sensitivity to 5-FU by assaying for the number of TS 5' UTR repeats. A 100% correlation between expression levels, number of TS 5' UTR repeats and response to 5-FU would not have been required. The ordinary artisan would have recognized that knowledge of the number of 5' UTR repeats would have allowed one to effectively identify subjects more likely or less likely to respond to

5-FU treatment. Thereby, the ordinary artisan would have been motivated to have generated, and would have had been more than a reasonable expectation of success of generating, a method for screening patients for sensitivity to 5-FU by assaying for the number of repeats in the TS 5' UTR region.

Regarding the Kawakami reference, it is asserted that this reference does not teach as broadly as suggested by the Office action. It is argued that Kawakami identified the 2R/2R genotype in only 2 of 68 patients and that a later publication by Dr. Danenberg (2004) questions the conclusions made by the Kawakami et al reference. These arguments and the teachings of the Danenberg (2004) reference have been fully considered but are also not persuasive. Kawakami reports that there was in fact a difference in the expression level of TS in patients having the 2R/2R, 2R/3R and 3R/3R genotypes. Kawakami found that TS levels in cancer tissues were higher in the order of the 3R/3R, 2R/3R and 2R/2R genotypes. Kawakami concluded that "(t)hese data demonstrated that the tandemly repeated sequence of the TS gene is polymorphic in gastrointestinal cancers and that its genotype is associated with TS protein expression. This association suggests that the TS genotype could be a new predictor of cancer patients' response to 5-FUra-based chemotherapy. "While the Danenberg reference may question the number of 2R/2R genotypes analyzed by Kawakami, there is nothing in the Danenberg (2004) reference which establishes that the findings of Kawakami are incorrect. In fact, Danenberg (page 2487) cites Uchida as teaching that TS expression was 1.5 fold higher in patients with the 3R/3R genotype as compared to patients with the 2R/2R genotype, thereby substantiating the findings of Kawakami. Applicants

appear to be requiring that the prior art meets a level of enablement that far exceeds that required for obviousness. Absolute predictability is not required to practice a method of screening to identify patients that are more likely or less likely to be senstive to a conventionally used chemotherapeutic drug. The fact that other variables may also influence a patient's response to 5-FU treatment does not negate the fact that the combined references when considered as a whole would have suggested the claimed method of screening patients to identify those patients with an increased likelihood of being sensitive to 5-FU treatment by assaying for the number of TS 5' UTR repeats. The cited prior art provides both the motivation to practice, and more than a reasonable expectation of success of practicing, a method of screening subjects for sensitivity to 5-FU by assaying for the number of TS 5' UTR repeats.

As stated *in Ex parte Kubin* (No. 2007-0819, Bd. Pat. App. & Int. May 31, 2007): "When there is motivation to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under 103. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct 1727, 82 USPQ2d 1385, 1397 (2007)." This reasoning is also applicable to the present situation wherein the prior art provides the motivation to obtain a method of identifying subjects more likely and less likely to be sensitive to 5-FU and provides a predictable solution to this problem – i.e., assaying for

the number of TS 5'UTR repeats as indicative of TS expression levels and thereby as indicative of sensitivity to 5-FU.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 47, 48, 52, 53, 56, 64 and 68-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 12 of copending Application No. 10/522,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope.

The instant claims are drawn to screening subjects for sensitivity to a TS-directed chemotherapeutic drug comprising genotyping a subject's biological sample for the 28 base pair repeat polymorphism in the 5'UTR of thymidylate synthase (TS) and

correlating the genotype to sensitivity to the drug. The claims include 5-FU, as well colorectal and gastric cancer. The claims ' 664 are drawn to selecting a therapeutic regimen for treating a cancer by screening a suitable cell or tissue sample for a polymorphism correlated with treatment outcome. When read in light of the specification, it is clear that the polymorphism includes "a tandemly repeated 28 base pair sequence in the thymidylate synthase gene's 5' UTR." Specifically, the '664 application teaches that "(p)atients less likely to be responsive to treatment with a TS directed drug, e.g., 5- fluorouracil, were determined to be homozygous for this triple repeat of the tandemly repeated sequence. Patients exhibiting heterozygous genotype for a double repeat and a triple repeat of the tandemly repeated sequence. The patients most likely to respond to administration of a TS directed drug (e.g., 5-fluorouracil) are homozygous for a double repeat of the tandemly repeated sequence." Further, as defined by the '664 specification, screening includes PCR analysis to identify the TS genotype.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 61-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 12 of copending Application No. 10/522,664 in view of Horie, Howells, and Govindarajan.

The teachings of '664 are set forth above. The claims of '664 are not specifically limited to any type of biological sample, such as bodily fluids, blood cells, or peripheral blood cells (claims 61-66). However, Horie teaches detecting the TS 5'UTR 28 base

pair repeat polymorphism in leukocytes of normal patients. Additionally, Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood, collected in EDTA, or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para). Further, Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Therefor, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a subject's normal cells, such as peripheral blood cells for the purpose of providing a less invasive method of determining a subject's TS genotype.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

14. In the response, Applicants "defer responding to these grounds of rejection until allowable subject matter has been indicated." However, the Office does not hold

rejections in abeyance until claims are indicated as otherwise allowable. Accordingly, the rejections are maintained and made final for the reasons stated above.

New grounds of rejection necessitated by Applicant's amendments to the claims:

Claim Rejections - 35 USC § 112 – second paragraph

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 70 is indefinite over the recitation of " said fluoropyrimidine" because this phrase lacks proper antecedent basis to the extent that claim 70 depends from claim 47. While claim 47 recites a TS-directed chemotherapy, the claim does not recite a fluoropyrimidine therapy. Further, the phrase "the patient" lacks proper antecedent basis to the extent that claim 70 depends from claim 47. While claim 47 refers to a human subject, claim 47 does not refer to a patient.

Conclusion

16. No claims are allowable over the cited prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634